



## Life Sciences Division

E-Newsletter August 24, 2007

### Highlights

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#### Low Dose Forum

Life Sciences Division scientists and research were prominently featured at the 13th International Congress of Radiation Research held in San Francisco, July 8-12. The Congress is a major forum for the discussion of radiation risk relevant to low dose exposures. **Eleanor Blakely** and **Amy Kronenberg** were members of the Organizing Committee and **Mary Helen Barcellos-Hoff** was on the Programme Committee. Dr. **Steve Chu** was a Congress Plenary Speaker, and **Joe Gray** and Barcellos-Hoff gave Congress Lectures, while **Andy Wyrobek**, Kronenberg, **Paul Spellman** and Blakely were symposia speakers. LBNL researchers also were active in poster presentations of their research in low dose and charged particle radiation biology. DOE was a notable supporter of the event. Congress website:

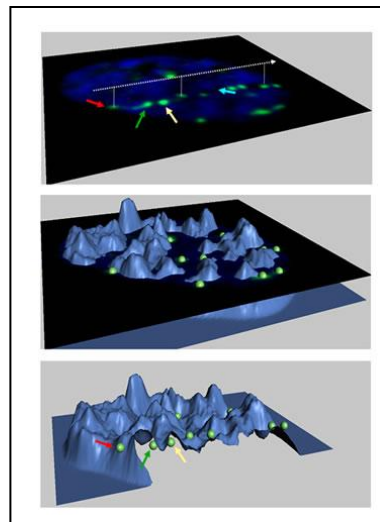
<http://www.sfconference.com/default.asp>

MHBH, 8/22/07

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#### Scientists Close in on DNA Repair Regions

Ionizing radiation, toxic chemicals, and other agents continually damage the body's DNA, threatening life and health: unrepaired DNA can lead to mutations, which in turn can lead to diseases like cancer. Intricate DNA repair mechanisms in the cells' nuclei are constantly working to fix what's broken, but whether the repair work happens "on the road"—right where the damage occurs—or "in the shop"—at specific regions of the nucleus—is unknown. Now, a team of researchers led by **Sylvain Costes** of the Life Sciences Division may be close to finding an answer.



The story about this research, funded by NASA Specialized Center of Research, can be found here: <http://www.lbl.gov/Science-Articles/Archive/LSD-broken-DNA.html>  
Today at Berkeley Lab, 8/7/07

Also covered in a UK report: [http://www.theregister.co.uk/2007/08/06/cell\\_damage\\_astronauts/](http://www.theregister.co.uk/2007/08/06/cell_damage_astronauts/)

The August edition of PLoS Computational Biology, in which this work is featured, will also feature Costes' figure on the cover: <http://compbiol.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pcbi.0030155&ct=>

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#### **Visit Barbara Lee**

On Tuesday, August 7, 2007, Berkeley Lab and UC Berkeley welcomed California's 9th Congressional District Congresswoman Barbara Lee for requested meetings on scientific research that deals with global climate change and energy, health, and education. She met with Lab Director Steve Chu and Molecular Foundry Director Carolyn Bertozzi, UC Berkeley Vice Chancellor for Research Beth Burnside as well as Acting Director of the Lab's Center for Science & Engineering Education Laurel Egenberger and UC Berkeley's California Teach Math and Science Initiative Nicole Nunes. Congresswoman Lee also engaged in discussions with the Lab and UCB's Helios and Biofuels research team, including Paul Alivisatos, Inez Fung, Chris Sommerville, Dan Kammen and Rick Diamond. In addition, she held discussions on public health issues with the Lab's **Joe Gray**, Director of Life Sciences Division, Thomas Rundall, Executive Associate Dean, and Denise Herd, Associate Dean at the UC Berkeley School of Public Health.

*Berkeley Lab Weekly Media Report, 8/10/07*

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#### **Bissell Wins 'Excellence in Science' Award**

**Mina Bissell** of Berkeley Lab's Life Sciences Division has been awarded the 2008 Excellence in Science Award from the Federation of the American Societies for Experimental Biology (FASEB). This award, sponsored by Eli Lilly and Company, recognizes outstanding achievement by women in the biological sciences. Bissell received the award for creating a "paradigm shift" in her conceptualization of the "dynamic reciprocity" between the cellular microenvironment, the extracellular matrix, and 3-D tissue structure in cell differentiation and cancer.

*Today at Berkeley Lab, 7/10/07*

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#### **Lab Employee Chosen as Regent Staff Advisor**

University of California President Robert Dynes Wednesday announced the selection of **William Johansen**, business manager for Berkeley Lab's Life Sciences Division, as the 2007-09 staff advisor to the UC Board of Regents. The staff advisor program allows for two staff to be selected to participate in open sessions of certain committees of the board. Staff advisors bring the voice and perspective of staff and non-Senate academic employees to board deliberations on relevant matters that come before the regents. Full story. Go here to read a feature story on Johansen that appeared in the February issue of The View: <http://www.lbl.gov/Publications/Currents/Archive/Feb-16-2007.html#3>  
<http://www.universityofcalifornia.edu/news/2007/jun27.html>

*Today at Berkeley Lab, 6/30/07*

## Recent publications (selected)

Yetta Porter-Chapmana, Edith Bourret-Courchesneb and **Stephen E. Derenzo**. Bi<sup>3+</sup> luminescence in ABiO<sub>2</sub>Cl (A=Sr, Ba) and BaBiO<sub>2</sub>Br, *Journal of Luminescence*, Article in Press, Corrected Proof, doi:10.1016/j.jlumin.2007.05.007, Available online 4 June 2007.

Trivalent bismuth luminescence is reported in three Sillen bismuth oxyhalide phases, SrBiO<sub>2</sub>Cl, BaBiO<sub>2</sub>Cl, and BaBiO<sub>2</sub>Br. These compounds exhibit Bi 6s<sub>6p</sub><sup>7</sup>6s<sub>2</sub> emission under UV and X-ray radiations. At room temperature, BaBiO<sub>2</sub>Cl shows the most intense light emission, with spectral and decay properties similar to those found in Bi<sub>4</sub>Ge<sub>3</sub>O<sub>12</sub> (BGO). At low temperatures, each phase show an increase in the photoluminescence intensities and a narrowing of the emission peaks. In contrast to the temperature dependence of BGO, X-ray excited luminescence intensities of all three phases remain relatively constant throughout the temperature range 10–295 K, though much lower than BGO at low temperatures. This result indicates that the Sillen phases undergo less thermal quenching than BGO. The low temperature and room temperature radio-luminescence decay times were determined from pulsed X-ray measurements. At room temperature, SrBiO<sub>2</sub>Cl exhibits faster decays than BGO, while BaBiO<sub>2</sub>Cl and BaBiO<sub>2</sub>Br have decay times similar to BGO.

Kenny PA, Lee GY, Myers CA, Neve RM, Semeiks JR, **Spellman PT**, Lorenz K, Lee EH, **Barcellos-Hoff MH**, Petersen OW, **Gray JW**, **Bissell MJ** (2007). The morphologies of breast cancer cell lines in three-dimensional assays correlate with their profiles of gene expression. *Molecular Oncology* 1(1): 84-96  
3D cell cultures are rapidly becoming the method of choice for the physiologically relevant modeling of many aspects of non-malignant and malignant cell behavior ex vivo. Nevertheless, only a limited number of distinct cell types have been evaluated in this assay to date. Here we report the first large scale comparison of the transcriptional profiles and 3D cell culture phenotypes of a substantial panel of human breast cancer cell lines. Each cell line adopts a colony morphology of one of four main classes in 3D culture. These morphologies reflect, at least in part, the underlying gene expression profile and protein expression patterns of the cell lines, and distinct morphologies were also associated with tumor cell invasiveness and with cell lines originating from metastases. We further demonstrate that consistent differences in genes encoding signal transduction proteins emerge when even tumor cells are cultured in 3D microenvironments.

**Kenneth H Downing** and Haixin Sui. Structural insights into microtubule doublet interactions in axonemes *Current Opinion in Structural Biology*, *Current Opinion*, Volume 17, Issue 2, April 2007, Pages 253-259.

Coordinated sliding of microtubule doublets, driven by dynein motors, produces periodic beating of eukaryotic cilia and flagella. Recent structural studies of the axoneme, which forms the core of cilia and flagella, have used cryo-electron tomography to reveal new details of the interactions between some of the multitude of proteins that form the axoneme and regulate its movement. Connections between the several types of dyneins, in particular, suggest ways in which their action might be coordinated. Study of the molecular architecture of isolated doublets has provided a structural basis for understanding mechanical properties related to the bending of the axoneme, and has also offered insight into the potential role of doublets in the mechanism of dynein activity regulation.

**Susan E Celniker** and Roger A Hoskins, Berkeley Drosophila Genome Project. *Drosophila by the dozen*, Genome Biology 2007, 8:309 doi:10.1186/gb-2007-8-7-309.

A report of the 48th Annual Drosophila Research Conference, Philadelphia, USA, 7-11 March 2007. <http://genomebiology.com/2007/8/7/309>

Tsutomu Shimura, Melvenia Martin, Michael J. Torres, Cory Gu, **Janice M Pluth**, Maria DeBernardi, Jeoffrey S. McDonald, and Mirit I. Aladjem . DNA-PK is Involved in Repairing a Transient Surge of DNA Breaks Induced by Deceleration of DNA Replication, J Mol Biol. 2007 March 30; 367(3): 665–680. doi: 10.1016/j.jmb.2007.01.018.

Cells that suffer substantial inhibition of DNA replication halt their cell cycle via a checkpoint response mediated by the PI3 kinases ATM and ATR. It is unclear how cells cope with milder replication insults, which are under the threshold for ATM and ATR activation. A third PI3 kinase, DNA-dependent protein kinase (DNA-PK), is also activated following replication inhibition, but the role DNA-PK might play in response to perturbed replication is unclear since this kinase does not activate the signaling cascades involved in the S-phase checkpoint. Here we report that mild, transient drug-induced perturbation of DNA replication rapidly induced DNA breaks that promptly disappeared in cells that contained a functional DNA-PK whereas such breaks persisted in cells that were deficient in DNA-PK activity. After the initial transient burst of DNA breaks, cells with a functional DNA-PK did not halt replication and continued to synthesize DNA at a slow pace in the presence of replication inhibitors. In contrast, DNA-PK deficient cells subject to low levels of replication inhibition halted cell cycle progression via an ATR-mediated S-phase checkpoint. The ATM kinase was dispensable for the induction of the initial DNA breaks. These observations suggest that DNA-PK is involved in setting a high threshold for the ATR-Chk1-mediated S-phase checkpoint by promptly repairing DNA breaks that appear immediately following inhibition of DNA replication.

<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1855631>

**Bo Hang** and Anton B. Guliaev. Substrate specificity of human thymine-DNA glycosylase on exocyclic cytosine adducts, Chemical Biological Interaction; v.165; no.3; pp.230-8; 02/20/2007

The environmental carcinogen glycidaldehyde (GDA) and therapeutic chloroethylnitrosoureas (CNU) can form hydroxymethyl etheno and ring-saturated ethano bases, respectively. The mutagenic potential of these adducts relies on their miscoding properties and repair efficiency. In this work, the ability of human thymine-DNA glycosylase (TDG) to excise 8-(hydroxymethyl)-3,N4-ethenocytosine (8-hm-C) and 3,N4-ethanocytosine (EC) was investigated and compared with C, a known substrate for TDG. When tested using defined oligonucleotides containing a single adduct, TDG is able to excise 8-hm-C but not EC. The 8-hm-C activity mainly depends on guanine pairing with the adduct. TDG removes 8-hm-C less efficiently than C but its activity can be significantly enhanced by human AP endonuclease 1 (APE1), a downstream enzyme in the base excision repair. TDG did not show any detectable activity toward EC when placed in various neighboring sequences, including the 5'-CpG site. Molecular modeling revealed a possible steric clash between the non-planar EC exocyclic ring and residue Asn 191 within the TDG active site, which could account for the lack of TDG activity toward EC. TDG was not active against the bulkier exocyclic adduct 3,N4-benzethenocytosine, nor the two adenine derivatives with same modifications as the cytosine derivatives, 7-hm-A and EA. These findings expand the TDG

substrate range and aid in understanding the structural requirements for TDG substrate specificity.

[http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&list\\_uids=17270163&cmd=Retrieve&indexted=google](http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed&list_uids=17270163&cmd=Retrieve&indexted=google)

Zhou S, Zhou H, Walian PJ, **Jap BK**. Regulation of gamma-Secretase in Alzheimer's Disease, *Biochemistry*. 2007 Mar 13;46(10):2553-63. Epub 2007 Feb 14.

The gamma-secretase complex is an intramembrane aspartyl protease that cleaves its substrates along their transmembrane regions. Sequential proteolytic processing of amyloid precursor protein by beta- and gamma-secretase produces amyloid beta-peptides, which are the major components of amyloid plaques in the brains of Alzheimer's disease patients. The gamma-secretase complex is therefore believed to be critical in the pathogenesis of Alzheimer's disease. Here we review the range of factors found to affect the nature and degree of gamma-secretase complex activity; these include gamma-secretase complex assembly and activation, the integral regulatory subunit CD147, transient or weak binding partners, the levels of cholesterol and sphingolipids in cell membranes, and inflammatory cytokines. Integrated knowledge of the molecular mechanisms supporting the actions of these factors is expected to lead to a comprehensive understanding of the functional regulation of the gamma-secretase complex, and this, in turn, should facilitate the development of novel therapeutic strategies for the treatment of Alzheimer's disease.